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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
POPA, ILEANA	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/652,814	UNGER, GRETCHEN M.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66-95,97-100,102-109,111-116,118, 119, 122-124, 126, 127 and 133-141* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66,87-94 and 133-141* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 68-86,95,97-100,102-109,111-116,118,119,122-124,126 and 127.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/26/2007 has been entered.

2. In the reply to the restriction requirement of 04/24/2006, Applicant elected with traverse (i) the invention of Group II, drawn to a composition comprising a surfactant associated with a bioactive component and a shell surrounding the association of bioactive component and surfactant, wherein the shell comprises at least one biocompatible polymer that provides specific cellular or tissue uptake and (ii) the species of proteinaceous material as biocompatible polymer; Applicant also cancelled claims 1-65, 96, 110, 117, 120, 121, 125, and 128-132 and withdrew claims 68-86, 103-109, 111-116, 118, 119, 122-124, 126, and 127. The reply was filed on 05/24/2006. In the non-final Office action of 06/14/2006, the Examiner withdrew claims 95, 97-100, and 102 as being drawn to non-elected species.

In the request for continued examination filed on 09/26/2007, Applicant cancelled claim 101, amended claims 66, 67, 94, 133, 134, and introduced new claims 137-141.

The status of the claims is as follows:

Claims 1-65, 96, 101, 110, 117, 120, 121, 125, 128-132 are cancelled, claims 68-86, 95, 97-100, 102-109, 111-116, 118, 119, 122-124, 126, 127 are withdrawn, and claims 137-141 are new. Claims 66, 67, 94, 133, and 134 have been amended.

Newly added claims are drawn to the elected invention.

Claims 66, 67, 87-94, and 133-141 are under examination.

3. All rejections pertaining to claim 101 are moot because Applicant cancelled the claim in the response filed on 09/26/2007.

4. The provisional rejection of claims 66, 67, 87, 88, 90, 92-94, 101, 133, 134, and 136 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, and 8 of copending Application No. 10/378,044 is withdrawn because Application No. 10/378,044 has been abandoned.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re*

Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 66, 67, 87, 88, 90, 94, 133, 134, and 136-141 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 25-28 of copending Application No. 11/622,359. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are drawn to a composition of nanocapsules comprising (i) a surfactant micelle consisting of a bioactive component that has a therapeutic effect and a surfactant having an HLB value of less than about 6.0, and (ii) a shell surrounding the surfactant micelle, wherein the shell comprises a precipitate containing a polypeptide and a cationic precipitating agent and wherein the polypeptide provides specific cellular by binding to cell surface antigens or receptors; the particles have an average diameter of less than 50 nm as measured by atomic force microscopy after drying of the particles (claims 66 and 139). The cation can be Li^+ (claims 94, 138, and 139), the polypeptide

comprises tenascin (claims 133, 134, 140, and 141), the bioactive component is a polynucleotide (claims 67 and 139) which can be associated with a nucleic acid condensing agent (claim 137), the surfactant has a HLB of less than 5.0 (claim 88) and can be a non-ionic (claim 87) or is selected from the group recited in claims 90 and 136.

The application claims drawn a collection of particles having a bioactive component, a surfactant with an HLB less than 6.0, a biocompatible polymer, and a cell recognition component having affinity for a cell receptor; the average diameter of the particles is less than 50 nm as measured by atomic force microscopy after drying of the particles (claim 25), wherein the bioactive component is a polynucleic acid (claim 28) and wherein the biocompatible polymer is tenascin claims 26 and 27). The specification defines that: **(i)** the surfactant can be a non-ionic surfactant or 2,4,7,9-tetramethyl-5-decyn-4,7-diol (i.e., a surfactant that has an HLB of less than 5.0, as recited in the instant claims 87, 88, 90, and 136), **(ii)** the particles comprise surfactant micelles containing surfactant and a bioactive agent, **(iii)** the biocompatible polymer forms a shell surrounding the surfactant micelles, and **(iv)** the biocompatible polymer is precipitated by cations such as Li^+ (p. 9. lines 21-23. p. 10, lines 1-21, p. 75, lines 15-18, p. 76, lines 3-13). With respect to the limitation of nanocapsule, the specification disclosed that the particles can be formulated as nanocapsules (p. 11, lines 6 and 7). With respect to the limitation of the polynucleotide being associated with a nucleic acid condensing agent, this is not innovative over the prior art, which teaches that condensing agents are always used when delivering nucleic acids via nanoparticles.

Thus, the application claims 25-28 anticipate the instant claims 66, 67, 87, 88, 90, 94, 133, 134, and 136-141. Since the claims of the Application No. 11/622,359 embrace all limitations of the instant claims, the application claims and the instant claims are obvious variants of one another.

Applicant argues that, since the instant application has an earlier filing date, the double patenting rejection should be withdrawn and made against the later filed application. In response to Applicant's argument it is noted that the provisional double patenting rejection must be made unless it is the only rejection remaining in one of the applications (see MPEP 822.01[R-3]). Since, in the instant case the double patenting rejection is not the only remaining rejection (see below), Applicant's argument is not found persuasive and the rejection is maintained.

7. Claims 66, 67, 87, 88, 90, 94, 133, 134, and 136-141 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10 and 13 of copending Application No. 10/958,999. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are drawn to a composition of nanocapsules comprising (i) a surfactant micelle consisting of a bioactive component that has a therapeutic effect and

a surfactant having an HLB value of less than about 6.0, and (ii) a shell surrounding the surfactant micelle, wherein the shell comprises a precipitate containing a polypeptide and a cationic precipitating agent and wherein the polypeptide provides specific cellular by binding to cell surface antigens or receptors; the particles have an average diameter of less than 50 nm as measured by atomic force microscopy after drying of the particles (claims 66 and 139). The cation can be Li^+ (claims 94, 138, and 139), the polypeptide comprises tenascin (claims 133, 134, 140, and 141), the bioactive component is a polynucleotide (claims 67 and 139), which can be associated with a nucleic acid condensing agent (claim 137), the surfactant has a HLB of less than 5.0 (claim 88) and can be a non-ionic (claim 87) or is selected from the group recited in claims 90 and 136.

The application claims recite a collection of particles comprising an agent, a surfactant molecule having an HLB of less than 6.0, a polymer soluble in aqueous solution, wherein the collection of particles has an average diameter of less than about 100 nm as measured by atomic force microscopy after drying and wherein the agent is an anti-sense nucleic acid (i.e., a polynucleotide) directed against protein kinase CK2beta (claim 10). The collection of particles further comprises a cell recognition agent (claim 13). The specification defines that the surfactant can be a non-ionic surfactant or 2,4,7,9-tetramethyl-5-decyn-4,7-diol, as recited in the instant claims 87, 88, 90, and 136 (i.e., a surfactant with an HLB of less that 5.0), the particles further comprise Li^+, wherein Li^+ is used to precipitate the biocompatible polymer that surrounds the micelles comprising the surfactant and bioactive agent, and the polymer can be tenascin (p. 12, lines 17-22, p. 13, lines 1-18, p. 47, lines 18-20, p. 70, Example

2, p. 79, lines 1 and 2). With respect to the limitation of nanocapsule, the specification defines that the particles can be formulated as nanocapsules (p. 14, lines 4 and 5). With respect to the limitation of the polynucleotide being associated with a nucleic acid condensing agent, this is not innovative over the prior art, which teaches that condensing are always used when delivering nucleic acids via nanoparticles.

Thus, the application claims 10 and 13 anticipate the instant claims 66, 67, 87, 88, 90, 94, 133, 134, and 136-141. Since the claims of the Application No. 10/958,999 embrace all limitation of the instant claims, the application claims and the instant claims are obvious variants of one another.

Applicant argues that, since the instant application has an earlier filing date, the double patenting rejection should be withdrawn and made against the later filed application. In response to Applicant's argument it is noted that the provisional double patenting rejection must be made unless it is the only rejection remaining in one of the applications (see MPEP 822.01[R-3]). Since, in the instant case the double patenting rejection is not the only remaining rejection (see below), Applicant's argument is not found persuasive and the rejection is maintained.

8. Claims 66, 67, 87, 88, 90, 93, 94, 133, 134, and 136-141 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29, 31, 33, 37, and 42 of U.S. Patent No. 6,632,671.

The instant claims are drawn to a composition of nanocapsules comprising (i) a surfactant micelle consisting of a bioactive component that has a therapeutic effect and a surfactant having an HLB value of less than about 6.0, and (ii) a shell surrounding the surfactant micelle, wherein the shell comprises a precipitate containing a polypeptide and a cationic precipitating agent and wherein the polypeptide provides specific cellular by binding to cell surface antigens or receptors; the particles have an average diameter of less than 50 nm as measured by atomic force microscopy after drying of the particles (claims 66 and 139). The cation can be Li^+ (claims 94, 138, and 139), the polypeptide comprises tenascin (claims 133, 134, 140, and 141), the bioactive component is a polynucleotide (claims 67 and 139) which can be associated with a nucleic acid condensing agent (claim 137), the surfactant has a HLB of less than 5.0 (claim 88), the surfactant can be non-ionic (claim 87) or is selected from the group recited in claims 90 and 136, the composition further comprises a water-miscible solvent (claim 93).

The patent claims recite a plurality of particles comprising a surfactant with an HLB less than 5.0, a bioactive hydrophobic component (i.e., a bioactive component), and a biocompatible polymer, wherein the particles have an average diameter of less than 50 nm as determined by atomic force microscopy and wherein the biocompatible polymer is precipitated in the presence of a cation (claims 29, 37, and 42). The surfactant can be a non-ionic surfactant or 2,4,7,9-tetramethyl-5-decyn-4,7-diol (claim 33), as recited in the instant claims 87, 90, and 136, and the particles further comprise a water-miscible solvent (claim 31). With respect to the limitation of the biocompatible polymer providing specific cellular uptake, the specification discloses that the

biocompatible polymer can be tenascin (see fig. 7B, and also column 3, lines 6-8). The specification discloses that the biocompatible polymer forms a shell surrounding the surfactant micelles containing the bioactive component and the surfactant, the hydrophobic bioactive component can be a polynucleic acid, and that the precipitating cation is Li^+ (Abstract, column 3, lines 25-32, column 5, lines 37-59, column 7, lines 32-37, column 9, lines 40-45, column 10, lines 42-66, column 15, lines 30-32). With respect to the limitation of HLB being less than 6.0, the patent claims recite an HLB less than 5.0 that anticipates the claimed HLB of less than 6.0. With respect to the limitation of nanocapsules, the specification discloses that the particles are formulated as nanocapsules (Abstract). With respect to the limitation of the polynucleotide being associated with a nucleic acid condensing agent, this is not innovative over the prior art, which teaches that condensing are always used when delivering nucleic acids via nanoparticles.

Therefore, the patent claims 29, 31, 33, 37, and 42 anticipate claims 66, 67, 87-94, 101, 133, and 134 of the instant application. Since the patent claims embrace all the limitation of the instant claims, the application claims and the instant claims are obvious variants of one another.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 66, 67, 87, 88, 90-94, 135, and 137-139 are rejected under 35 U.S.C. 102(e) as being anticipated by Unger et al. (US Patent No. 6,139,819, of record), as evidenced by Kondo et al. (Anal Chem, 1991, 198: 30-35, Abstract).

Unger et al. teach particles comprising a core provided by monomolecular layers of surfactant micelles consisting of a surfactant such as cetyl alcohol (i.e., a non-ionic surfactant having an HLB less than 5.0) and a bioactive agent which has a therapeutic effect, wherein the surfactant micelles are stabilized by a surrounding protein shell ; the protein shell is covalently coupled with targeting ligands that bind cell surface receptors (i.e., the protein provides specific cellular uptake), wherein the covalent coupling involves the formation of Schiff base linkages which are reduced by using lithium aluminum hydride (claims 66, 87, 88, 90, 94, 135, 138, and 139) (column 6, lines 52-61, column 8, lines 1-3 and 44-47, column 14, lines 10-12, column 15, lines 62-65, column 16, lines 18-26, column 17, line 60, column 18, line 61, column 30, lines 18-32 , 66, and 67, column 31, lines 29 and 30, column 34, lines 24-49, column 38, lines 13-17, column 48, lines 43-45, column 49, lines 1-8, column 59, lines 66 and 67, column 60, lines 1-4 and 16-24). Unger et al. teach that the bioactive agent could be a polynucleic acid which is associated with cationic lipids (i.e., a condensing agent) (claims 67 and 137) (column 9, lines 36-50, column 10, lines 13-23, column 60, lines 16-21). Unger et al. teach their particles as having a hollow core comprising the bioactive agent (column 60,

lines 1-4 and 16-24), i.e. they teach nanocapsules (see also Applicant's definition of nanocapsules, on p. 5, lines 21-24 of the instant specification). Unger et al. also teach that the particles have a size of about 30 nm (claims 66 and 139) (column 28, lines 51-53), that the particles can comprise a combination of two or more surfactants (claim 91) (column 19, lines 21-25, column 31, lines 52-57), a biocompatible oil, such as peanut oil (claim 92) (column 33, lines 23-25), and a water-miscible solvent (claim 93) (Example 4). With respect to the limitation of the protein shell being precipitated by the cation, wherein the cation is Li^+ (claims 66 and 139), this is inherent to the nanocapsules of Unger et al., since the covalent attachment of the targeting ligand requires addition of lithium aluminum hydride (see above), which would necessarily result in a precipitated protein shell (it is noted that Li^+ is known in the art as a protein precipitating agent, see for example Kondo et al., Abstract). Since Unger et al. teach all the limitations of the instant claims, the claimed invention is anticipated by the above-cited art.

Applicant argues that the particles taught by Unger et al. do not include a cation-precipitated shell containing a polypeptide and Li^+ and that they teach stabilization as either being derived from a covalent association of the bioactive agent and other components, or incorporation of PEG, which stabilizes due to high molecular weight and hydrophilic properties. Applicant argues that PEG methods in particular result in liposomes larger than the claimed particles. With respect to the limitation of Li^+, Applicant argues that Unger et al. do not teach Li^+ as a precipitating agent and it is not taught that the shell comprises a precipitate of Li^+ and a polypeptide. Applicant argues

that lithium carbonate is only taught as a generic salt for a gaseous precursor or that lithium aluminum hydride is only taught as producing covalent Schiff linkages. Applicant argues that the invention of Unger et al. is related to contrast agents for diagnostic and therapeutic use in conjunction with ultrasound (Abstract), while the instant invention is drawn to a cell-targeted nanocapsule containing a therapeutic agent associated with a surfactant, surrounded by a cation-precipitated polypeptide, wherein the nanocapsule is useful for efficient intracellular delivery. Applicant argues that the Examiner relied on disparate sections in the disclosure of Unger et al. and picked a number of different options disclosed by the reference, such as: **(i)** picking the non-ionic hydrophobic cetyl alcohol from the 120 disclosed lipids, wherein the majority of the disclosed lipids are hydrophilic (column 17, lines 23-29, column 21, lines 64-67); in contrast to the instant invention which requires hydrophobic lipids, **(ii)** picking a protein as a stabilizing compound from a list that includes any material (column 31, lines 1-43), **(iii)** picking the size of 30 nm from a wide range of 30 nm to 100μm (column 28, lines 51-53).

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

With respect to the argument that the particles taught by Unger et al. do not include a cation-precipitated shell containing a polypeptide and Li^+, see above. With respect to the argument that Unger et al. do not specifically teach a precipitated shell, it is noted that this limitation is an inherent property of particles of Unger et al., which comprise a protein shell and a targeting ligand, wherein the binding of the targeting ligand to the protein shell requires the presence of Li^+ (see above). The argument that

Unger et al. teach stabilization as either being derived from a covalent association of the bioactive agent and other components or from incorporation of PEG is incorrect. Unger et al. clearly teach that the bioactive agent is incorporated into the core of surfactant micelles and that the surfactant micelles (and not the bioactive agent) are stabilized by surrounding them with a protein shell (column 11, lines 59-65, column 14, lines 10-13, column 30, lines 18-25, 66, and 67, column 31, lines 29 and 30, column 60, lines 1-24); PEG is just an embodiment of the genus of stabilizing biocompatible polymers, which clearly encompasses proteins (see above). Applicant's argument that the use of PEG results in liposomes larger than the claimed particles is just an argument not supported by any substantiation; Applicant did not provide any evidence to support this assertion. Even if this would be true, Unger et al. clearly make a distinction between protein-coated surfactant micelles and liposomes and teach that both could be used in their method (column 27, lines 35-37, column 60, lines 41-43). Applicant's argument that the invention of Unger et al. is only related to contrast agents for diagnostic and therapeutic use in conjunction with ultrasound is not found persuasive. Unger et al. clearly teach therapy, wherein therapy is in conjunction with imaging; their particles are targeted to tissues in the body for diagnostic imaging and/or administration of bioactive agents, i.e., therapy can be achieved in the absence of imaging (column 1, lines 20-25, column 8, lines 44-47). Regardless whether imaging is used or not, similar to the claimed invention, the nanocapsules of Unger et al. are cell-targeted delivery vehicles, comprising micelles having a bioactive agent associated with a hydrophobic surfactant, wherein the micelles are surrounded by a cation-precipitated protein shell. Additionally,

Unger et al. teach their nanocapsules as being suitable for the intracellular delivery of DNA (column 115, Example 42). With respect to picking the non-ionic hydrophobic cetyl alcohol from the 120 disclosed lipids, it is noted that Unger et al. teach a variety of both hydrophilic and hydrophobic lipids (or surfactants), wherein the hydrophilic lipids do not constitute the majority, as Applicant asserts (column 17, lines 60-67, column 18, lines 1-67, column 19, lines 1-8); the argument that the list of lipids is long is irrelevant, since, similar to the instant claims and specification, Unger et al. disclose the use of various hydrophobic lipids as suitable for their vesicles, wherein cetyl alcohol is one of these lipids (see MPEP 2131.02 - A REFERENCE THAT CLEARLY NAMES THE CLAIMED SPECIES ANTICIPATES THE CLAIM NO MATTER HOW MANY OTHER SPECIES ARE NAMED and 2123 [R5] I—PATENTS ARE RELEVANT FOR PRIOR ART FOR ALL THEY CONTAIN). Therefore, Unger et al. clearly teach the limitation of cetyl alcohol (claim 90). Similar considerations apply to picking a protein as a stabilizing compound from a list that includes any material (Unger et al. clearly teach protein to coat and stabilize the surfactant micelles, see above), and to picking the size of 30 nm from a wide range of 30 nm to 100μm; with respect to the size, it is noted that, beside the range of 30 nm-100μm, Unger et al. clearly teach the specific embodiments of 30 nm and 12 nm (column 28, lines 60-62).

In addition to the above, in response to Applicant's discussion that the instant invention is distinct from the prior art because the instant nanocapsules deliver the therapeutics to the nucleus due to their small size of less than 50 nm (thus crucially avoiding lysosomal degradation), it is noted that, since the nanocapsules of Unger et al.

are identical to the instant nanocapsules, they must necessarily have the same property, i.e., direct delivery of therapeutics to the nucleus of the target cell. Therefore, Applicant's argument that the prior art teaches that the ordinary fate of non-viral delivery vehicles upon internalization is fusion with lysosomes is not found persuasive. Even Applicant's argument that the instant nanocapsules are targeted to the nucleus only because they are smaller than 50 nm is evidence that the nanocapsules of Unger et al., which are less than 30 nm in size, would have the same property.

In conclusion, the nanocapsules of Unger et al. are identical to the instant nanocapsules, and therefore, Unger et al. anticipate the claimed invention.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 66, 67, 87, 88-94, 133-135, and 137-141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger et al. taken with Kondo et al., in view of Schneider et al. (FEBS Letters, 1998, 429: 269-273, of record).

The teachings of Unger et al. anticipate claims 66, 67, 87, 88, 90-94, 135, and 137-139. Briefly, Unger et al. teach nanocapsules comprising a core provided by monomolecular layers of surfactant micelles consisting of a surfactant such as cetyl

alcohol (i.e., a non-ionic surfactant having an HLB less than 5.0) and a bioactive agent which has a therapeutic effect, wherein the surfactant micelles are stabilized by a surrounding lithium-precipitated protein shell ; the protein shell is covalently coupled with targeting ligands that bind cell surface receptors (i.e., the protein provides specific cellular uptake), wherein the covalent coupling involves the formation of Schiff base linkages which are reduced by using lithium aluminum hydride (claims 66, 87, 88, 90, 94, 135, 138, and 139). Unger et al. teach that the bioactive agent could be a polynucleic acid which is associated with cationic lipids (i.e., a condensing agent) (claims 67 and 137), that the nanocapsules have a size of about 30 nm (claims 66 and 139), that the nanocapsules can comprise a combination of two or more surfactants (claim 91), that the nanocapsules further comprise a biocompatible oil, such as peanut oil (claim 92) and a water-miscible solvent (claim 93). Kondo et al. provide evidence that the presence of Li^+ in the composition of Unger et al. necessarily results in a precipitated protein shell.

However, Unger et al. do not teach tenascin (claims 133, 134, 140, and 141) or a critical micelle concentration of about 200 micromolar (claim 89). Schneider et al. teach identification of a polypeptide derived from the C-terminus of tenascin (claims 133 and 140) capable to bind to $\alpha_9\beta_1$ integrins on the cell surface, i.e., Schneider et al. also teach a ligand that targets a receptor for tenascin (claims 143 and 141) (Abstract, p. 272, column 2 first paragraph and Fig. 4). Schneider et al. also teach their peptide as being suitable to mediate specific gene delivery to $\alpha_9\beta_1$ integrin-expressing cells (Abstract, p. 269, column 2, second paragraph, p. 272, column 2, second and third paragraphs). It

would have been obvious to one of skill in the art, at the time the invention was made to modify the nancapsules of Unger et al. by replacing their targeting ligands with the peptide of Schneider et al. with the intent to target the particles to $\alpha_9\beta_1$ integrin-expressing cells, with a reasonable expectation of success. The motivation to do so is provided by Schneider et al., who teach that targeting $\alpha_9\beta_1$ integrin is promising for the development of gene therapy delivery vehicles since $\alpha_9\beta_1$ integrin is highly expressed on human airway epithelia irrespective of any clinical status (p. 269, column 1 bridging column 2). One of ordinary skill in the art would have been expected to have a reasonable expectation of success in making such particles because Unger et al. teach that peptide ligands can be successfully included in their nanocapsules. With respect to the limitation of the surfactant having a critical micelle concentration of about 200 μm (claim 89), absent evidence of unexpected results, if the general conditions of a given method are disclosed in the prior art, it would have been obvious to the ordinary skilled artisan to vary the parameters in a given method with the purpose of optimizing the results, i.e., to use a surfactant with the desired critical micelle concentration according to the intended use of the particles. Again, absent evidence to the contrary, it is generally not inventive to discover the optimal working conditions of a prior art method, such conditions can be identified by routine experimentation. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that, based on the art, the particles of Unger et al. containing a gas are not intended to release the contents, but rather to deliver the contents to an

extracellular location via ultrasound energy, which is in contrast to the claimed invention, which teaches intracellular delivery without application of ultrasound energy. Applicant also argues that modifying the particles of Unger et al. according to the teachings of Schneider et al. would make them undesirable for their intended purpose, since it would increase their rigidity and make them less susceptible to destruction via ultrasound energy; such particles would require undesirable high levels of ultrasound energy, which would increase the risk of damage to the patient's tissue. The rest of Applicant's arguments are the same as above.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

As noted in the response to the arguments above, Unger et al. teach embodiments wherein their particles do not comprise a gas, wherein the particles are targeted to specific cells by specific agents that target cell surface receptors and antigens which would necessarily result in particle internalization and intracellular delivery of therapeutic agents (column 8, lines 44-47, column 38, lines 13-67, column 39, lines 1-67). Even in the embodiment wherein the particles do contain a gas, Unger et al. teach intracellular delivery of DNA using gas-filled particles without ultrasound; the use ultrasound results in localized delivery at the site the ultrasound was applied, as opposed to general delivery in the absence of ultrasound (column 115, Example 42). Applicant's argument that modifying the particles according to the teachings of Schneider et al. would make them undesirable for their intended purpose is again an argument that is not supported by any evidence. Unger et al. clearly teaches particle

coated with precipitated proteins (see above) that are suitable for their method. With respect to the rest of the arguments, see above.

13. Claims 66, 67, 87, 88, 90-94, and 135-139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger et al. taken with Kondo et al., in view of each Medina (U.S. Patent No. 5,650,543, of record), Quay (U.S. patent No. 5,707,606, of record), and Duquemin et al. (J Pharm Pharmacol, 1985, 37: 698-702, Abstract).

The teachings of Unger et al. anticipate claims 66, 67, 87, 88, 90-94, 135, and 137-139. Briefly, Unger et al. teach nanocapsules comprising a core provided by monomolecular layers of surfactant micelles consisting of a surfactant such as cetyl alcohol (i.e., a non-ionic surfactant having an HLB less than 5.0) and a bioactive agent which has a therapeutic effect, wherein the surfactant micelles are stabilized by a surrounding lithium-precipitated protein shell ; the protein shell is covalently coupled with targeting ligands that bind cell surface receptors (i.e., the protein provides specific cellular uptake), wherein the covalent coupling involves the formation of Schiff base linkages which are reduced by using lithium aluminum hydride (claims 66, 87, 88, 90, 94, 135, 138, and 139). Unger et al. teach that the bioactive agent could be a polynucleic acid which is associated with cationic lipids (i.e., a condensing agent) (claims 67 and 137), that the nanocapsules have a size of about 30 nm (claims 66 and 139), that the nanocapsules can comprise a combination of two or more surfactants (claim 91), that the nanocapsules further comprise a biocompatible oil, such as peanut oil (claim 92) and a water-miscible solvent (claim 93). Kondo et al. provide evidence

that the presence of Li^+ in the composition of Unger et al. necessarily results in a precipitated protein shell.

However, Unger et al. do not teach acetylenic diols (claim 136). Medina teaches the acetylenic diol 2,4,7,9-tetramethyl-5-decyne-4,7-diol (i.e., the species recited in claim 136) and its ethoxylates as excellent surfactants because of their ability to decrease the surface tension (Abstract, column 1, lines 30-35, column 3, lines 3-5). Medina does not teach using their 2,4,7,9-tetramethyl-5-decyne-4,7-diol for the fabrication of nanoparticles. However, Quay teaches the use of acetylenic diols or blends thereof for the preparation of stable and biocompatible colloidal dispersions used for enhancing the contrast in an ultrasound image (Summary of the invention, column 3, lines 15-19, column 7, lines 9-16). Based on the teachings of Quay one of skill in the art would have known that acetylenic diols could be used to obtain biocompatible particles suitable for the delivery of bioactive agents. Based on the teachings of Medina (i.e., the ability to decrease the surface tension), one of skill in the art would have known that the use of acetylenic diols such as 2,4,7,9-tetramethyl-5-decyne-4,7-diol would result in small particles that are more efficient in delivering bioactive components. It is noted that one of skill in the art would have known that reducing the surface tension would result in smaller particles because the prior art teaches this (see for example Duquemin et al., Abstract). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the particles of Unger et al. by using 2,4,7,9-tetramethyl-5-decyne-4,7-diol, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Medina clearly teaches that 2,4,7,9-

tetramethyl-5-decyne-4,7-diol is able to decrease the surface tension. One of skill in the art would have been expected to have a reasonable expectation of success in making such a composition because the art teaches that acetylenc diols can be successfully used in the preparation of particles for the *in vivo* delivery of agents. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Medina and Quay fail to remedy the deficiencies of Unger et al. Applicant argues that Medina does not distinguish the ethoxylated acetylenic diols by hydrophobic or hydrophilic properties. Applicant argues that Quay teaches ethoxylated acetylenic diols for colloidal dispersions for enhancing contrast and that it is known in the art that ethoxylated acetylenic diols can have HLB values from 4 to 17, depending on ethoxyl concentration. Applicant continues arguing that Quay discloses that reducing surface tension does not necessarily result in smaller particle size (Example 5). Therefore, Applicant argues, neither Medina nor Quay suggests the desirability of the claimed combination.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

With respect to Medina, the argument that the reference ethoxylated acetylenic diols can have HLB values from 4 to 17 is not found persuasive because the reference does not distinguish the ethoxylated acetylenic diols by hydrophobic or hydrophilic properties is not found persuasive because Medina teaches the claimed 2,4,7,9-tetramethyl-5-decyne-4,7-diol is not ethoxylated (see above), which must have an HLB

of less than 6.0. With respect to Quay, he teaches a strong dependence of particle size stability on surface tension (column 18, Example 14), which is in agreement with the teachings of the prior art (see above). In Example 5 Quay teaches that the use of sodium perfluorocarbonate does not result in smaller size only because sodium perfluorocarbonate is highly anionic and generation of high anionic charge density at the emulsion interface prevents the formation of small particles. This is a special case, which does not support Applicant's argument of unpredictability, since Quay clearly teaches that lowering surface tension results in higher particle size stability for all surfactants tested, with the exception of highly anionic surfactants (Example 14). Based on these teachings, one of skill in the art would know to avoid highly anionic surfactants, and not acetylenic diols such as 2,4,7,9-tetramethyl-5-decyne-4,7-diol. With respect to the deficiencies of Unger et al., see above.

14. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Ileana Popa, PhD

Art Unit 1633